PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PU4828WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US 03/17347	International filing date *(day/month/year)* 03.06.2003	Priority date *(day/month/year)* 04.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/7076		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the International application

Date of submission of the demand	Date of completion of this report
11.12.2003	02.08.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Zimmer, B Telephone No. +49 89 2399-8600

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/17347

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-15 as originally filed

Claims, Numbers

1-31 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 25 and 26 with regard to industrial applicability

   because:

   ☒ the said international application, or the said claims Nos. 25 and 26 with regard to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,3,6,11-13,16-19
	No:	Claims	1,4,5,7-10,14,15,20-31
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-31
Industrial applicability (IA)	Yes:	Claims	1-24,27-31
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 25 and 26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art.34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

The present application contains separate groups of inventions:

invention 1:	claims 1-22 and 25-31:	pharmaceutical compositions comprising abacavir, lamivudine and a highly compressible carrier as well as their method of preparation and therapeutic use
invention 2:	claims 23 and 24:	method for maintaining high drug loading in a pharmaceutical composition by including a highly compressible carrier

The problem to be solved by invention 1 is the provision of an oral pharmaceutical formulation comprising lamivudine and abacavir which is uniform and of appropriate hardness and has a high drug loading.
This is solved by a pharmaceutical formulation comprising a pharmaceutically acceptable highly compressible carrier.

The problem to be solved by invention 2 is the provision of a method for maintaining high drug loading in a pharmaceutical composition. This is solved by including a highly compressible carrier in said formulation.

The two inventions are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The common technical feature linking inventions 1 and 2 is the presence of a highly

compressible pharmaceutical carrier, such as highly compressible microcrystalline cellulose, in pharmaceutical compositions.
The presence of highly compressible microcrystalline cellulose as a carrier in pharmaceutical compositions is known in the prior art (see D1, D2, D4 and D6).

Therefore, the requisite unity of invention (Rule 13.1 PCT) no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of invention 1 and invention 2.

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: WO 00/ 16779
   D2: WO96/ 30025 (cited in the application)
   D3: WO 99/ 55372
   D4: XP009006009
   D5: XP001154010
   D6: XP009015365

2. Novelty

   Prior art document D1 discloses a tablet comprising abacavir, lamivudine and Avicel PH101 as a highly compressible pharmaceutical carrier (ex. 1; formulation B) and a similar composition is disclosed in D2 (ex. 1, formulation B).
   A tablet comprising abacavir hemisulfate, lamivudine and microcrystalline cellulose is further described in D3 (ex. 2).
   In view of the above cited prior art, the subject-matter of claims 1, 4, 5, 7-10, 14, 15, 20-22 and 25-31 does not meet the requirements of Art. 33(2) PCT.

3. Inventive Step

3.1 Inventive step cannot be assessed when the requirements of novelty are not met. However, in the light of the above cited prior art, it appears that the problem underlying the present patent application lies in the provision of a tablet containing abacavir (or a pharmaceutically acceptable derivative thereof) and lamivudine (or a pharmaceutically acceptable derivative thereof), which is uniform and of appropriate hardness and has a high drug loading (see p. 2, l. 22-27). The claimed subject-matter relates, in the light of the above cited prior art to an obvious solution of the problem (Art. 33(3) PCT).

3.2 Dependent claims 2, 3 and 11-13 do not appear to contain any additional features which involve an inventive step when combined with the subject-matter of any claim to which they refer. Dependent claims are only allowable when related to a patentable independent claim (Rule 6.4 PCT).

3.3 Although the subject-matter of claims 6 and 16-18 disclosing compositions comprising Ceolus® microcrystalline cellulose appears to be new in view of the cited prior art it is not inventive.
D1, which is regarded as closest prior art discloses Avicel PH101 as a highly compressible carrier in pharmaceutical formulations comprising abacavir and lamivudine instead of Ceolus® microcrystalline cellulose.
Thus, in view of the cited prior art, the technical problem seems to be the provision of an alternative carrier for a pharmaceutical composition comprising abacavir and lamivudine with improved hardness and uniformity.
In view of D5 disclosing Ceolus® as exhibiting a higher compressibility in tablets than Avicel® PH 101 (p. 164, left col., last para.) the subject-matter of claims 6 and 16-18 seems to be obvious for a person skilled in the art and does not involve an inventive step (Art. 33(3) PCT).

4. The subject-matter of invention 2 is neither novel nor inventive in view of prior art document D6 disclosing Avicel PH 101 as an excipient in high drug loaded theophylline spheres (p. 949, right col., last para.), which leads to a strong bonding in tablets (D4: p. 133, left col.).

5. Further remarks

5.1 The term "highly compressible" frequently used in the independent and dependent claims is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Art. 6 PCT).

5.2 The expression "substantially" employed in claim 12 sets unclear hints to the scope claimed. It is unclear what the actual concentration of the corresponding (+)-enantiomer is and in respect of which criteria it should be understood. To overcome said objection the definition given on p. 7, l. 19ff should be cited instead. Furthermore, the term "about" frequently used in the claims is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of the claims unclear (Art. 6 PCT).

5.3 There does not seem to be a difference between the subject-matter of claims 16 and 17 as the terms "comprising" and "consisting essentially" are regarded to be equal (Art. 6 PCT).

5.4 Claim 15 is not supported by the description as required by Art 6 PCT.
Claim 2 discloses a tablet hardness of greater than 18 kilopounds whereas the description states a value of 20 kilopounds at 25 kilonewton force (p. 4, l. 20, 21); furthermore, claim 9 discloses an amount of 15 to 1500 mg lamivudine whereas the description states a rang of 15 to 100 mg (p. 11, l. 1).

5.5 Claims 2 and 3 comprise all the features of claim 1 and are therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).

5.6 As the expressions "hereby incorporated by reference" and "not limited to" frequently used in the description as well as the paragraph on p.15 are not deleted in the description the requirements of Rules 5 and 9.1 PCT are not met.

6. For the assessment of the present claims 25 and 26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter

of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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